REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claims 39, 41, 42, and 73 have been canceled without prejudice or disclaimer of the subject matter recited therein. Further, claims 32, 40, 44, 48-51, 53, 57, 58, 65 and 74-77 have been amended to further clarify the claimed invention. Support for the amendments can be found throughout the specification. In particular, support for amended claim 32 can be found on page 6, lines 1-6, and page 8, lines 1-5, of the specification. Support for amended claim 44 can be found on page 6, lines 1-6 and on page 8, lines 5 and 15-24 of the specification. Accordingly, no new matter has been added.

I. Claim Objection

Claim 44 has been objected to for reciting "fro" in line 3 instead of "for," and claim 53 has been objected to for having a comma at the end of the sentence instead of a period. Claims 44 and 53 have been amended to correct these typographical errors.

II. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 32-44 and 46-80 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly

claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner has stated that independent claims 32 and 44 are directed to a composition comprising one or more recombinant vectors that encode at least one early polypeptide and at least one late polypeptide from a papillomavirus, with the exception of a DNA sequence encoding the specific combination of E7 and L2. Dependent claims 39-42 state that the early polypeptide is E6 and/or E7 and the late polypeptide is L1 and/or L2. Further, the Examiner has stated that independent claim 65 recites a composition including one late and one early papillomavirus polypeptide, which encompasses the specifically excluded combination of E7 and L2. Based thereon, the Examiner has concluded that the compositions are contradictory in the independent claims and it is unclear as to which papillomavirus polypeptides are intended to be expressed by the vector-based compositions.

This rejection is rendered moot in light of the amendments to the claims, in particular claims 32 and 44.

The Examiner has also considered that claim 32 is confusing because line 1 recites that the composition comprises one or more vectors, but lines 7-8 recite that the composition does not comprise one or more vectors. Applicants submit that claim 32 is directed to a vector-based composition encoding early and late papillomavirus polypeptides, but containing no vector encoding a polypeptide having immunostimulatory activity. However, in order to expedite prosecution in the subject application and not acquiesce to

the Examiner's rejection, Applicants have amended claim 32 rendering this portion of the rejection moot.

Finally, the Examiner has stated that the term "variant" found in claims 57 and 58 lacks antecedent basis. In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claim 40, from which claims 57 and 58 depend, to recite "nononcogenic variants . . . ." Support for the amendment can be found on page 4, line 38 to page 5, line 6 of the subject specification.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 32-44 and 46-80 under 35 U.S.C. § 112, second paragraph.

III. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 32-44 and 46-64 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner has stated that the language excluding the DNA sequences encoding the specific combination of L2 and E7 polypeptides of human papillomavirus is not supported by the original disclosure. Therefore, the Examiner has argued that this limitation is new matter. In order to expedite prosecution in the subject application and not

acquiesce to the Examiner's rejection, Applicants have amended claims 32 and 44 to no longer recite the exclusionary language.

The Examiner has rejected claim 32 for reciting additional exclusionary language. Again, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claim 32 to no longer recite the exclusionary language.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 32-44 and 46-64 under 35 U.S.C. § 112, first paragraph.

IV. Rejection Under 35 C.F.R. § 102(e)

Claims 32-34, 39-43, 53 and 54 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Stanley et al. (U.S. Patent 6,096,869). Applicants respectfully traverse this rejection.

The Examiner has maintained that the teachings of Stanley et al. anticipate the present claims because the open language "comprising" permits other ingredients into the composition, such as IL-12. In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended the claims.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 32-34, 39-43, 53 and 54 under 35 U.S.C. § 102(e).

V. Rejections Under 35 U.S.C. § 103(a)

Claims 44, 46, 48, 49, 52, 55, 56, 59, 60, 65-67, 72-74 and 78-80 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Stanley et al., as applied to claims 32-34, 39-43, 53 and 54 above, and further in view of Hines et al. (*Obstetrics and Gynecology*, 1995, Vol. 86, No. 5, pp. 860-866). Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden by showing, first, that the cited prior art coupled with the general knowledge at the time of the invention must contain some suggestion or incentive to motivate a skilled artisan to modify or combine references. *See In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the Examiner must show that the modification or combination of prior art references must have a reasonable expectation of success (at the time of the invention). *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the Examiner must show that the cited or combined references teach each and every limitation of the claims. *See In re Zurko,* 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Stanley et al. teach a composition comprising a vaccinia vector encoding at least one papillomavirus polypeptide (E1, E2, E4, E5, E6, E7, L1 and/or L2) together with IL-12.

Hines et al. discloses a pharmaceutical composition intended for the treatment of papillomavirus-induced diseases relying on HPV-16 E7-derived peptides or cytotoxic T lymphocytes *in vitro* stimulated by an HPV early peptide and IL-2 (in other words a cellular composition).

Essentially, the Examiner's position is that, at the time the invention was made, one skilled in the art would have been motivated to express IL-2 in the composition of Stanley et al. to stimulate a cellular immune response against papillomavirus tumor formation *in vivo*. More specifically, the Examiner has argued that IL-2 expression into the vector-based composition encoding papillomavirus polypeptides would allow one to eliminate the time-consuming step of extracting, stimulating and re-administrating peripheral blood lymphocytes back in patients; to eliminate the possibility of contaminating the patient's lymphocytes before re-administration; to control the amount of expression of the cytokine and to increase opportunities for the cytokine to stimulate more T cells than would be possible to isolate from a single extraction for *ex vivo* stimulation in culture.

To support the rejection, the Examiner raises potential problems (see preceding paragraph) associated with the cellular adoptive therapy protocol disclosed by Hines et al. However, it is noted that all of these problems are hypothetical, as no evidence has been provided by Hines et al. which would raise significant questions that the cellular adoptive therapy cannot be effectively used for treating or preventing papillomavirus-induced tumors. Quite to the contrary, Hines et al. discussed that administration of cytotoxic T lymphocytes stimulated *in vitro* with HPV early polypeptides is a useful therapeutic

modality to accelerate tumor regression. Based thereon, one skilled in the art had no reason to search for another alternative (e.g., expressing IL-2 from the vector-based composition encoding papillomavirus polypeptides), since Hines et al. recognized cellular adoptive therapy as efficient to treat papillomavirus-induced tumors. Moreover, it is further stated that "the rational for the therapy (cellular adoptive therapy) is that controlled *in vitro* stimulation of lymphocytes is more likely to yield effective anti-tumor responses compared to the response generated by the host *in vivo*." (Emphasis added). See the end of page 862 of Hines et al. Therefore, Hines et al. teaches away from the present invention which relies on the expression of specified HPV polypeptides and a cytokine such as IL-2 to generate an immune response by the host *in vivo*. In this regard, the Examiner is directed to Example 6 of the instant application which clearly shows that administration of a vaccinia virus expressing E6, E7, L1 and L2 papillomavirus polypeptides and IL-2 achieves prophylactic and therapeutic immunization in animal models against HPV-induced tumors.

In conclusion, there is no reasonable basis for concluding that one skilled in the art would have been motivated to express IL-2 in a papillomavirus composition (e.g., that of Stanley et al.) to replace the cellular adoptive therapy protocol of Hines et al. First, the cited references support the view that the person skilled in the art would consider the cellular adoptive therapy as suitable to treat papillomavirus-induced tumors. Second, none of the cited references teach or suggest any significant problems that would have motivated one skilled in the art to search for an alternative approach. In this respect, Applicants point out that it is unrealistic and improper to address potential hypothetical problems and

hypothetical therapeutic end points suggested by the Examiner (i.e., eliminating the time-consuming step of extracting, stimulating and re-administrating peripheral blood lymphocytes back in patients; eliminating the possibility of contaminating the patient's lymphocytes before re-administration; controlling the amount of expression of the cytokine and increasing opportunities for the cytokine to stimulate more T cells than would be possible to isolate from a single extraction for *ex vivo* stimulation in culture) that are not even suggested in the cited references.

Moreover, Stanley et al. teaches the administration of IL-12 to enhance the immune response against a papillomavirus tumor formation, based on the experimental observation that IL-12 is present in 100% of regressing HPV-induced lesions whereas normal cervix samples and non-regressing lesions are exempt of IL-12 transcripts. The administration of IL-12 can be associated with one or more papillomavirus polypeptides (among a choice of 8 early and late polypeptides) or vectors expressing one or more papillomavirus polypeptides. First, Stanley et al. does not disclose the specific combinations of papillomavirus polypeptides which are now the subject matter of the amended claims. With respect to cytokines, Stanley et al. also studied the transcription of IL-2 in cervical tissues obtained from normal women (table e of Stanley et al.), from HPV-infected patients with either regressing (table d of Stanley et al.) or non-regressing lesions (tables a, b and c of Stanley et al.). Normal cervix showed transcripts for IL-2 (table e of Stanley et al.), as well as the majority of the regressing genital lesions (4/5 table d of Stanley et al.). IL-2 expression is also observed in some of the non-regressing lesions (5/8 in table c, 2/7 in table b and 0/8 in

table a of Stanley et al.). Thus, the pattern of expression of IL-2 is quite different to the one observed for IL-12 (exclusive expression in regressing lesions). Therefore, the teachings of Stanley et al. do not motivate one skilled in the art to express IL-2 instead of IL-12 to stimulate a cellular immune response against papillomavirus tumor formation.

The combination of these references fails to render the present invention obvious because neither reference, singly or in combination, suggests the combination of the papillomavirus polypeptides which are now specifically claimed. Moreover, reading Stanley et al., one skilled in the art would not be motivated to use IL-2 instead of IL-12, as described above.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 44, 46, 48, 49, 52, 55, 56, 59, 60, 65-67, 72-74 and 78-80 under 35 U.S.C. § 103(a).

Claim 47 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Stanley et al. and Hines et al., as applied to claims 32-34, 39-44, 46, 48, 49, 52-56, 59, 60, 65-67, 72-74 and 78-80 above, and further in view of Gajewski (*The Journal of Immunology*, 1996, Vol. 156, pp. 465-472). Applicants respectfully traverse this rejection.

The deficiencies of Stanley et al. and Hines et al. have been discussed above.

Gajewski relates to B7.1-induced stimulation of naive lymphocytes to cytotoxic T lymphocytes (CTL). To this end, the B7.1 cDNA was transfected into P815 mastocytoma cells. Mouse splenocytes were then stimulated with the transfected cells in the presence of an anti-CD3 antibody. B7.1 transfected tumor cells stimulated proliferation of CD4+ as well as CD8+ T cells. As discussed on page 470 of Gajewski, direct costimulation of

CD8+ T lymphocytes by expression of B7.1 allows emergence of CTL that produce their own IL-2. It is suggested that expression of B7.1 on human tumor cells can render them better able to stimulate CD8+ lymphocytes and that utilization of B7.1-expressing autologous tumor cells may provide a plausible immunization approach for cancer patients.

Applicants submit that this rejection should not apply to the composition of amended claim 47 which is directed to the expression of E6, E7, L1 and L2 papillomavirus polypeptides together with B7.1 as the immunostimulatory polypeptide. None of the cited references, singly or in combination, disclose this specific combination of papillomavirus polypeptides. Moreover, the inclusion of B7.1 immunostimulatory molecule in the vector-based composition is not suggested in Gajewski, which is primarily directed to the use of B7.1-stimulated human tumor cells to treat cancer.

Therefore, Applicants respectfully request withdrawal of the rejection of claim 47 under 35 U.S.C. § 103(a).

Claims 35-37, 61-63 and 68-70 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Stanley et al. and Hines et al., as applied to claims 32-34, 39-44, 46, 48, 49, 52-56, 59, 60, 65-67, 72-74 and 78-80 above, and further in view of Boursnell et al. (WO 92/16636). Applicants respectfully traverse this rejection.

The deficiencies of Stanley et al. and Hines et al. have been discussed above.

Boursnell et al. teaches a recombinant virus vector expressing wild-type or functional portions of E6 and E7 proteins from HPV strains 16 and 18, for treating or preventing conditions caused by an HPV infection. More specifically, Boursnell et al.

illustrates a recombinant vaccinia virus of the Wyeth strain containing the nucleotide sequences encoding E6 and E7 polypeptides from both HPV-16 and HPV-18, which are fused to form a single open reading frame (E6/E7 protein) and placed under the control of a promoter, each expression cassette being placed in opposite direction with respect to one another to avoid recombination events.

The Examiner's position is that one of ordinary skill in the art at the time the invention was made would have been motivated to use the Wyeth strain as the vector to encode the papillomavirus polypeptides. But the purpose of the invention is not the vector as such, but the vector(s) expressing the specified polypeptide combinations. The vector is a means to express the claimed combination and therefore the invention may encompass the use of well known virus vectors such as the Wyeth strain of vaccinia. As none of the cited references, singly or in combination, disclose the claimed specific polypeptide combinations, the vector(s) encoding such combinations is thus novel and inventive. It is Applicants' understanding that, if independent claims are considered as patentable over the cited references, the patentability will also apply to the dependent claims.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 35-37, 61-63 and 68-70 under 35 U.S.C. § 103(a).

Claims 38, 64 and 71 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Stanley et al. and Hines et al., as applied to claims 35-37, 61-63 and 68-70 above, and further in view of Meyer et al. (*Journal of General Virology*, 1991, 72:1031-1038). Applicants respectfully traverse this rejection.

The deficiencies of Stanley et al. and Hines et al. have been discussed above.

Meyer et al. relates to general technology associated with MVA. As stated above, the purpose of the invention is not the vector as such, but the vector(s) expressing the specified polypeptide combinations. The vector is a means to express the claimed combination and therefore the invention may encompass the use of well known virus vector such as the MVA strain of vaccinia. As none of the cited references, singly or in combination, disclose the claimed specific polypeptide combinations, the vector(s) encoding such combinations is thus novel and inventive.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 38, 64 and 71 under 35 U.S.C. § 103(a).

Claims 50, 51, 57, 58 and 75-77 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Stanley et al. and Hines et al., as applied to claims 32-34, 39-44, 46, 48, 49, 52-56, 59, 60, 65-67, 72-74 and 78-80 above, and further in view of Crook et al. (*Cell*, 1991, 67:547-556) and Munger et al. (*The EMBO Journal*, 1989, 8:4099-4105). Applicants respectfully traverse this rejection.

The deficiencies of Stanley et al. and Hines et al. have been discussed above.

Crook et al. teaches nononcogenic variants of E6 papillomavirus polypeptide and Munger et al. teaches nononcogenic variants of E7 papillomavirus polypeptide. Applicants note that these two references are cited throughout the specification in connection with the nononcogenic variants. See page 5, line 4; page 18, line 30 and page 19, line 5, of the specification. Here again, the purpose of the present invention is not the nononcogenic

variants as such, but the specified polypeptide combinations. As none of the cited references, singly or in combination, disclose the claimed specific polypeptide combinations, the claims are thus novel and inventive.

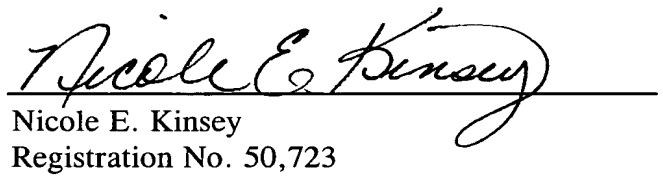
Therefore, Applicants respectfully request withdrawal of the rejection of claims 50, 51, 57, 58 and 75-77 under 35 U.S.C. § 103(a).

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 
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Date: April 2, 2002

Attachment to Amendment dated April 2, 2002
Marked-up Claims

32. (Twice Amended) A composition consisting of [comprising] one or more recombinant vectors into which are inserted [(i) at least one] DNA sequences [sequence] coding for the [an] early E6 and E7 polypeptides [polypeptide] of a papillomavirus and [(ii) at least one] DNA sequences [sequence] coding for the [a] late L1 and L2 polypeptides [polypeptide] of a papillomavirus[, with the exception of the specific combination of DNA sequence coding for the E7 early polypeptide and of DNA sequence coding for the L2 late polypeptide of human papillomavirus]; said DNA sequences being placed under the control of the elements necessary for their expression in a host cell or organism [and wherein said composition does not comprise one or more recombinant vectors into which are inserted DNA sequences coding for at least one polypeptide having an immunostimulatory activity].

40. (Twice Amended) The composition of claim 32, wherein said E6 and E7 polypeptides are [early polypeptide is a] nononcogenic variants of the native E6 and [and/or] E7 polypeptides [polypeptide] of a papillomavirus.

44. (Twice Amended) A composition consisting of (i) [comprising] one or more recombinant vectors into which are inserted [(i) at least one] DNA sequences [sequence] coding for the [an] early E6 and E7 polypeptides [polypeptide] of a papillomavirus and [(ii) at least one] DNA sequences [sequence] coding for the [fro a] late L1 and L2 polypeptides

[polypeptide] of a papillomavirus[, with the exception of the specific combination of DNA sequence coding for te E7 early polypeptide and DNA sequence coding for the L2 late polypeptide of human papillomavirus]; said DNA sequences being placed under the control of the elements necessary for their expression in a host cell or organism and (ii) [further comprising] one or more recombinant vectors into which [are] is inserted a DNA sequence [sequences] coding for [at least] one polypeptide having an immunostimulatory activity wherein said DNA sequence is [sequences are] placed under the control of the elements necessary for its [their] expression in a host cell or organism and wherein said polypeptide having an immunostimulatory activity is selected from the group consisting of interleukin-2, interleukin-7, the co-adhesion molecule B7.1 and the co-adhesion molecule B7.2.

48. (Twice Amended) The composition of claim 44, [comprising] consisting of one [or more] recombinant vector [vectors] into which [are] is inserted:

(a) a DNA sequence coding for the E6 polypeptide of a papillomavirus, a DNA sequence coding for the E7 polypeptide of a papillomavirus, a DNA sequence coding for the L1 polypeptide of a papillomavirus, a DNA sequence coding for the L2 polypeptide of a papillomavirus and a DNA sequence coding for the co-adhesion molecule B7.1, or

(b) a DNA sequence coding for the E6 polypeptide of a papillomavirus, a DNA sequence coding for the E7 polypeptide of a papillomavirus, a DNA sequence coding for the L1 polypeptide of a papillomavirus, a DNA

sequence coding for the L2 polypeptide of a papillomavirus and a DNA sequence coding for interleukin-2[, or

(c) a DNA sequence coding for the E6 polypeptide of a papillomavirus, a DNA sequence coding for the E7 polypeptide of a papillomavirus, a DNA sequence coding for the LI polypeptide of a papillomavirus, a DNA sequence coding for the L2 polypeptide of a papillomavirus, a DNA sequence coding for the co-adhesion molecule B7.1 and a DNA sequence coding for interleukin-2].

49. (Amended) The composition of claim 48, wherein said E6 and E7 polypeptides [polypeptide] are, respectively, nononcogenic variants of the native E6 and E7 polypeptides of a human papillomavirus.

50. (Amended) The composition of claim 49, wherein said nononcogenic variant of the E6 polypeptide is the native [a] HPV-16 E6 polypeptide deleted of amino acids 111-115.

51. (Amended) The composition of claim 49, wherein said nononcogenic variant of the E7 polypeptide is the native [a] HPV-16 E7 polypeptide deleted [cf] of amino acids 21-26.

53. (Amended) A method for the treatment or prevention of dysplasia or cancer of the neck of the uterus, comprising administering an effective amount of the composition of claim 43 to a patient in need of such treatment.[,]

57. (Amended) The composition of claim 40, wherein said nononcogenic variant of the E6 polypeptide is the native [a] HPV-16 E6 polypeptide deleted of amino acids 111-115.

58. (Amended) The composition of claim 40, wherein said nononcogenic variant of the E7 polypeptide is the native [a] HPV-16 E7 polypeptide deleted of amino acids 21-26.

65. (Amended) A composition consisting of [comprising] one or more recombinant vectors into which are inserted (i) [at least one] DNA sequences [sequence] coding for the E6 polypeptide of a papillomavirus and for the E7 polypeptide of a papillomavirus [a polypeptide from an early or late region of a papillomavirus] and (ii) [at least] one DNA sequence coding for a polypeptide having an immunostimulatory activity; said DNA sequences being placed under the control of the elements necessary for their expression in a host cell or organism and wherein said polypeptide having an immunostimulatory activity is selected from the group consisting of interleukin-2, interleukin-7, the co-adhesion molecule B7.1 and the co-adhesion molecule B7.2.

74. (Amended) The composition of claim 65, consisting of [73, comprising] one [or more] recombinant vaccinia virus from the Copenhagen or MVA strain into which [are] is inserted a DNA sequence coding for the E6 polypeptide of HPV-16, a DNA sequence coding for the HPV-16 E7 polypeptide and a DNA sequence coding for interleukin-2.

75. (Amended) The composition of claim 65 [73], wherein said E6 and E7 polypeptides [polypeptide] are, respectively, nononcogenic variants of the native E6 and E7 polypeptides of a human papillomavirus.

76. (Amended) The composition of claim 75, wherein said nononcogenic variant of the E6 polypeptide is the native [a] HPV-16 E6 polypeptide deleted of amino acids 111-115.

77. (Amended) The composition of claim 75, wherein said nononcogenic variant of the E7 polypeptide is the native [a] HPV-16 E7 polypeptide deleted of amino acids 21-26.